(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 September 2015 (03.09.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/127558 A1

(51) International Patent Classification:
A61K 31/506 (2006.01) *C07C 215/64* (2006.01)
A61K 31/135 (2006.01) *C07C 229/36* (2006.01)
A61K 31/198 (2006.01) *C07C 271/44* (2006.01)
A61K 31/27 (2006.01) *C07D 215/38* (2006.01)
A61K 31/47 (2006.01) *C07D 401/12* (2006.01)
A61P 25/00 (2006.01)

(21) International Application Number:
PCT/CA2015/050146

(22) International Filing Date:
27 February 2015 (27.02.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/946,097 28 February 2014 (28.02.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

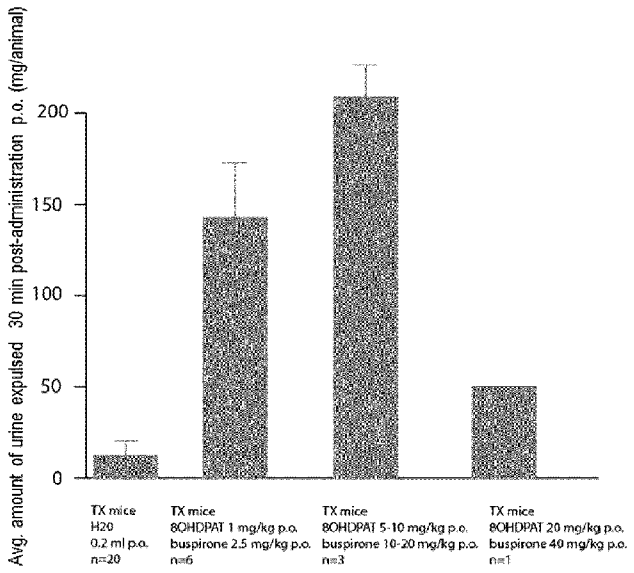
— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: METHODS AND USES FOR INDUCING OR FACILITATING MICTURITION IN A PATIENT IN NEED THEREOF

Figure 10



(57) Abstract: Compositions for eliciting acute micturition (voiding activity) in subjects having a spinal cord injury (SCI subject) are described herein. The compositions may generally comprise one or more of a 5-HT (5-hydroxytryptamine, serotonin) receptor agonist, a parasympathomimetic agent, a glutamate receptor agonist, and a noradrenaline/dopamine precursor. More specifically, the compositions may comprise one or more of: a 5-HT1A receptor agonist; a 5 HT1A/7 receptor agonist; a 5-HT2/3 receptor agonist; a cholinesterase inhibitor; an NMDA receptor agonist; and a noradrenaline/dopamine precursor. Uses and methods relating to eliciting acute micturition in subjects in need thereof are also described.

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METHODS AND USES FOR INDUCING OR FACILITATING MICTURITION IN A PATIENT IN NEED THEREOF

Spinal cord injury (SCI) generally leads to an immediate and irreversible loss of sensation and voluntary motor control below the level of injury, as well as to a rapid development of severe health problems such as osteoporosis, muscle atrophy, immune deficiency, hormonal dysregulation, infertility, autonomic dysreflexia, diabetes, obesity, cardiovascular complications, sexual dysfunction and bowel and bladder control problems.

SCI may occur following a trauma (e.g., car accident, sports, falls, etc.) or a disease (e.g., multiple sclerosis, spinal stenosis, spinal vascular accidents, etc.). Other comparable neurological disorders such as benign prostatic hyperplasia have also been associated with comparable dysfunction of bladder control induced by neural impairment.

Urination, also called micturition, is the process of disposing urine from the urinary bladder through the urethra to the outside of the body. The process of urination is usually under voluntary control. Physiologically, micturition involves coordination between the central, autonomic and somatic nervous systems. When control over urination is lost or absent, this is called urinary incontinence. However, for incompletely understood reasons, in patients with SCI of traumatic or non-traumatic origin, as well as in those suffering of comparable neurological disorders (e.g., benign prostatic hyperplasia or BPH), the opposite problem is typically found - urine retention also called continence (incapacity to empty the bladder).

Specifically, muscles involved in micturition such as those activating the bladder, urethra and pelvic floor are under the control of coordinated actions of the spinal micturition center (lumbosacral spinal cord) and the pontine micturition center (brain) among other neural structures. A simplified picture would be that as the bladder fills, sensory receptors in the bladder wall trigger the micturition motor behaviour - a simultaneous contraction of the detrusor and relaxation of the urethral and periurethral muscles.

In SCI patients, micturition can be improved with different methods such as bladder drainage (with chronic indwelling catheters), anticholinergic, alpha-adrenergic or cholinergic drugs, electrostimulation of sacral anterior roots for urine elimination, as well as diapers, condom sheaths or onabotulinumtoxin A injection (in bladder – e.g., detrusor muscle) for those specifically experiencing also associated mild incontinence. However, most of these approaches have been associated with problems including constipation, dry mouth and blurred vision (currently used drugs), urinary tract infections, frequent hospitalization and scepticemia (catheters), bladder cancer (infrequent urination), impaired sexual function (electrostimulations), etc.

SCI is an important market in neurology in North America and elsewhere. In the 70s, Statistics from the University of Alabama (The National Spinal Cord Injury Statistical Center in the U.S.) provided estimates of the incidence and prevalence of traumatic SCI in the U.S. Forty cases per million population was reported as a fair estimate of incidence. Accordingly 259,000 Americans living with SCI was then considered as a fair estimate of prevalence (www.spinalcord.uab.edu). However, more recently, an extensive study sponsored by the Christopher and Dana Reeve Foundation has reported very different estimates. According to that recent report, the incidence is similar to previous

estimates although the prevalence is significantly higher (e.g., than estimates from the University of Alabama) with 1,275,000 SCI patients (0.4% of the U.S. population)(www.christopherreeve.org). Consequently, SCI is likely to constitute the second most important neurological problems in the U.S. after Alzheimer's disease (approximately 4-5 million patients). Based on these new prevalence estimates, it is fair to consider the worldwide prevalence to conservatively range between 10 and 20 million SCI patients. Since multiple sclerosis constitutes also a market (300,000-400,000 patients in North America, probably 3-5 million patients worldwide, http://www.wrongdiagnosis.com /m/multiple_sclerosis/prevalence.htm; http://www.mult-sclerosis.org/ms_world.html) largely associated with comparable micturition problems (urine retention), it may constitute a significant secondary market for this promising technology. The prevalence of histologic benign prostatic hyperplasia (BPH) is estimated at 90% among men in the eighth decade of life.

Thus, the development of innovative solutions aimed at specifically inducing or promoting micturition safely and regularly (e.g., once or twice daily) in patients with urine retention problems would fulfill a poorly addressed medical need of SCI patients.

SUMMARY

In some aspects, the present description relates to a composition that may comprise: (a) a 5-HT1A receptor agonist; (b) a 5 HT1A/7 receptor agonist; (c) a 5-HT2/3 receptor agonist; (d) a cholinesterase inhibitor; (e) an NMDA receptor agonist; (f) a noradrenaline/dopamine precursor; or (g) any combination of (a) to (f), and optionally a pharmaceutically acceptable excipient or carrier, for inducing or facilitating micturition in a subject. In some embodiments, the composition may comprise at least two, at least three, or at least four of (a) to (f). In some embodiments, the composition may comprise a 5-HT1A receptor agonist, a 5 HT1A/7 receptor agonist, or both a 5-HT1A receptor agonist and a 5 HT1A/7 receptor agonist.

In some embodiments, the 5-HT1A receptor agonist may be: (1) buspirone; (2) tandospirone; (3) cannabidiol; (4) F-15,599; (5) flesinoxan; (6) gepirone; (7) ipsapirone; (8) quetiapine; (9) trazodone; (10) yohimbine; (11) indole alkaloid; (12) asenapine; (13) vortioxetine; (14) ziprasidone; (15) a pharmaceutically acceptable derivative of any one of (1)-(14); or (16) any combination of (1)-(15). More specifically, the 5-HT1A receptor agonist may be buspirone, or a pharmaceutically acceptable derivative thereof.

In some embodiments, the 5-HT1A/7 receptor agonist may be: (1) 8-OH-DPAT; (2) 5-CT; (3) a pharmaceutically acceptable derivative of (1) or (2); or (4) any combination of (1)-(3). More specifically, the 5-HT1A/7 receptor agonist may be 8-OH-DPAT, or a pharmaceutically acceptable derivative thereof.

In some embodiments, the composition may comprise a 5-HT2/3 receptor agonist. In some embodiments, the composition may comprise a 5-HT2/3 receptor agonist which is: (1) quipazine; (2) SR57227A; (3) LSD; (4) mescaline; (5) psilocin; (6) DMT; (7) 2C-B; (8) lorcaserin; (9) 2-methyl-5-HT; (10) BZP; (11) RS-56812; (12) a pharmaceutically acceptable derivative of any one of (1)-(11); or (13) any combination of (1)-(12). In some embodiments, 5-HT2/3 receptor agonist may be quipazine, or a pharmaceutically acceptable derivative thereof.

In some embodiments, the composition may comprise a cholinesterase inhibitor. In some embodiments, the cholinesterase inhibitor may be: (1) neostigmine; (2) physostigmine; (3) pyridostigmine; (4) rivastigmine; (5) any derivative of (1) to (4); or (6) any combination of (1)-(5). In some embodiments, the cholinesterase inhibitor may be neostigmine or a pharmaceutically acceptable derivative thereof.

In some embodiments, the composition may comprise an NMDA receptor agonist. In some embodiments, the NMDA receptor agonist may be: (1) N-methyl-D-aspartate (NMDA); (2) aminocyclopropanecarboxylic acid; (3) D-cycloserine; (4) cis-2,3-piperidinedicarboxylic acid; (5) L-aspartate; (6) quinolinate; (7) homocysterate; (8) D-serine; (9) ACPL; (10) L-alanine; (11) GLYX-13; (12) 3,5-dibromo-L-phenylalanine; (13) any pharmaceutically acceptable derivative of (1) to (12); or (14) any combination of (1)-(13). In some embodiments, the NMDA receptor agonist may be NMDA.

In some embodiments, the composition may comprise a noradrenaline/dopamine precursor, or a noradrenaline/dopamine precursor and a decarboxylase inhibitor. In some embodiments, the noradrenaline/dopamine precursor may be: (1) L-DOPA or L-DOPA/carbidopa; (2) phenylalanine; (3) tyrosine; (4) L-threo-3,4-dihydroxyphenylserine; (5) any pharmaceutically acceptable derivative of (1) to (4); or (6) any combination of (1)-(5).

In some embodiments, the composition may comprise 8-OH-DPAT or a pharmaceutically acceptable derivative thereof, and buspirone or a pharmaceutically acceptable derivative thereof.

In some embodiments, the composition may be for oral administration and may comprise 2.5 to 50 mg of buspirone, and/or 5 to 150 mg of neostigmine.

In some aspects, the present description relates to the use of a composition as defined herein for acutely inducing or facilitating micturition in a subject. In some aspects, the present description relates to the use of a composition as defined herein for the manufacture of a medicament for acutely inducing or facilitating micturition in a subject.

In some aspects, the present description relates to the use of: (a) a 5-HT1A receptor agonist; (b) a 5 HT1A/7 receptor agonist; (c) a 5-HT2/3 receptor agonist; (d) a cholinesterase inhibitor; (e) an NMDA receptor agonist; (f) a noradrenaline/dopamine precursor; or (g) any combination of (a) to (f), for inducing or facilitating micturition in a subject in need thereof. In some embodiments, (a) to (f) are compounds as defined herein (e.g., in **Table 1**, or pharmaceutically acceptable derivatives thereof). In some embodiments, the use may be for inducing or facilitating acute micturition in a subject in need thereof.

In some embodiments of the compositions or uses described herein, the subject may suffer from urinary retention. In some embodiments, the subject may be a spinal cord injury (SCI) subject. In some embodiments, the SCI subject may be a multiple sclerosis (MS) or Parkinson's disease (PD) subject.

In some embodiments, the compositions described herein may be for administration by a route which is: oral; parenteral; or sublingual.

In some embodiments, the compositions described herein may be for daily administration to the subject.

In some aspects, the present description relates to a method for inducing or facilitating acute micturition in a subject, the method comprising administering to the subject the composition as defined herein.

In some aspects, the present description relates to a kit comprising the composition as defined herein; and a suitable container.

In some aspects, the present description relates to the use of one or more agent, wherein the agent is: a 5HT2/3 receptor agonist, a 5HT1A receptor agonist, a 5-HT1A/7 receptor agonist, a noradrenaline/dopamine precursor, an NMDA receptor agonist, or a cholinesterase inhibitor for inducing or facilitating micturition (e.g., acutely inducing or facilitating micturition) in a patient in need thereof. In some embodiments, the above use may further comprise the use of a further therapeutic agent indicated for the treatment of spinal cord injuries or multiple sclerosis.

In some aspects, the present description relates to the use of a combination of one or agent, wherein the agent is: a 5HT2/3 receptor agonist, a 5HT1A receptor agonist, a 5-HT1A/7 receptor agonist, a noradrenaline/dopamine precursor, an NMDA receptor agonist, or a cholinesterase inhibitor, and a further therapeutic agent indicated for the treatment of spinal cord injuries or multiple sclerosis for inducing or facilitating micturition (e.g., acutely inducing or facilitating micturition) in a patient in need thereof.

In some aspects, the present description relates the use of one or more agent, wherein the agent is: a 5HT2/3 receptor agonist, a 5HT1A receptor agonist, a 5-HT1A/7 receptor agonist, a noradrenaline/dopamine precursor, a NMDA receptor agonist, or a cholinesterase inhibitor for the preparation of a medicament for inducing or facilitating micturition (e.g., acutely inducing or facilitating micturition) in a patient in need thereof.

In some aspects, the present description relates to a composition that may comprise one or more agent, wherein the agent is: a 5HT2/3 receptor agonist, a 5HT1A receptor agonist, a 5-HT1A/7 receptor agonist, a noradrenaline/dopamine precursor, a NMDA receptor agonist, or a cholinesterase inhibitor, and optionally a pharmaceutically acceptable excipient or carrier for inducing or facilitating micturition (e.g., acutely inducing or facilitating micturition) in a patient. In some embodiments, the composition may comprise a further therapeutic agent indicated for the treatment of spinal cord injuries or multiple sclerosis.

In some aspects, the present description relates to a method for inducing or facilitating micturition comprising administering one or more agent, wherein the agent is: a 5HT2/3 receptor agonist, a 5HT1A receptor agonist, a 5-HT1A/7 receptor agonist, a noradrenaline/dopamine precursor, a NMDA receptor agonist, or a cholinesterase inhibitor, to a patient in need thereof. In some embodiments, the method may further comprise administering a further therapeutic agent indicated for the treatment of spinal cord injuries or multiple sclerosis. In some embodiments, the patient may be an SCI patient. In some embodiments, the patient may be an MS patient.

In some embodiments, the agent described herein may be as defined in **Table 1**.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Histological examination and confirmation of spinal cord transection in a mouse. (A) A typical Th9/10 transection without staining. (B) Another luxol blue and cresyl violet stained cord clearly showing complete transection at the site of lesion.

Figure 2A and 2B: Summary of drug screening studies on incidence of micturition activity in non-acclimated spinal cord transected (Tx) mice within 30 min post-administration of different classes and subclasses of agents. Results from drugs administered i.p. separately are shown. In Fig. 2A: **(1)** quipazine; **(2)** L-DOPA/carbidopa; **(3)** NMDA; **(4)** clenbuterol; and **(5)** pilocarpine. In Fig. 2B: **(1)** 8-OH-DPAT; **(2)** buspirone; **(3)** DOI; **(4)** 7-OH-DPAT; **(5)** quipazine; **(6)** TFMPP; **(7)** L-DOPA/carbidopa; **(8)** clenbuterol; **(9)** clonidine; **(10)** moxonidine; **(11)** oxymetazoline; **(12)** NMDA; **(13)** A68930; **(14)** quipirole; **(15)** PD168077; **(16)** salbuterol; **(17)** TRH; **(18)** GR73632; **(19)** GR64349; **(20)** tizanidine; **(21)** midodrine; **(22)** SR57227A; **(23)** guanfacine; **(24)** methoxamine; **(25)** pilocarpine; **(26)** neostigmine; **(27)** physostigmine (n = 1); **(28)** AS19; and **(29)** H_2O (control).

Figure 3: Effect of s.c. administration of different classes and subclasses of agents on the expressed amounts (mg) of urine within 30 min post-administration to acclimated Tx mice. Groups tested: **(1)** water (vehicle); **(2)** quipazine; **(3)** buspirone; **(4)** 8-OH-DOPAT; and **(5)** neostigmine. Animals per group (drug) or subgroup (dose) > 10 spinal cord-transected female mice typically tested either at 7, 14, 21 or 28 days post-Tx.

Figure 4: Effect of s.c. administration of various subtypes of serotonergic (5-HT) receptor agonists on the expressed amounts (mg) of urine within 30 min post-administration to acclimated Tx mice. Drugs administered separately include: AS19 (5-HT7 receptor agonist); SR57227 (5-HT3 receptor agonist); quipazine (5-HT2/3 receptor agonist); buspirone (5-HT1A receptor agonist); and 8-OH-DPAT (5-HT1A/7 receptor agonist).

Figure 5: Dose-response micturition effects with buspirone administered s.c. to acclimated Tx mice. Doses tested include 1 mg/kg and 3 mg/kg buspirone.

Figure 6: Dose-response micturition effects with buspirone administered p.o. to acclimated Tx mice. Doses tested include 2.5 mg/kg and 10 mg/kg buspirone.

Figure 7: Dose-response micturition effects with 8-OH-DPAT administered s.c. to acclimated Tx mice. Doses tested include 0.5, 1, and 5 mg/kg 8-OH-DPAT.

Figure 8: Micturition effects with 8-OH-DPAT (1 mg/kg) administered p.o. to acclimated Tx mice.

Figure 9: Dose-response micturition effects with buspirone and 8-OH-DPAT administered simultaneously s.c. to acclimated Tx mice. Doses tested include 0.5 mg/kg 8-OH-DPAT + 1 mg/kg buspirone; and 1 mg/kg 8-OH-DPAT + 1 mg/kg buspirone.

Figure 10: Dose-response micturition effects with buspirone and 8-OH-DPAT administered simultaneously p.o. to acclimated Tx mice. Doses tested include: 1 mg/kg 8-OH-DPAT + 2.5 mg/kg buspirone; 5-10 mg/kg 8-OH-DPAT + 10-20 mg/kg buspirone; and 20 mg/kg 8-OH-DPAT + 40 mg/kg buspirone.

Figure 11: Effects of other drug combinations delivered via s.c. administration to acclimated Tx mice. Combinations tested include: **(1)** water (control); **(2)** Clenbuterol + Quipazine + GR64349; **(3)** 8-OH-DPAT + SR57227 + Quipazine; **(4)** 8-OH-DPAT + Quipazine + SR57227 + L-DOPA/carbidopa; **(5)** Clenbuterol + Quipazine + 8-OH-DPAT; **(6)** Clenbuterol + 8-OH-DPAT; **(7)** Neostigmine + 8-OH-DPAT; and **(8)** Neostigmine + Buspirone.

DESCRIPTION

The present inventor has surprisingly found that compositions comprising certain classes of drugs/compounds (or combinations thereof) may be able to elicit acute micturition (voiding activity) in subjects having a spinal cord injury (SCI subject). The compositions may generally comprise one or more of a 5-HT (5-hydroxytryptamine, serotonin) receptor agonist, a parasympathomimetic agent, a glutamate receptor agonist, and a noradrenaline/dopamine precursor. Preferably, the compositions described herein comprise compounds which can cross the blood-brain barrier.

The use of the word "**a**" or "**an**" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one" but it is also consistent with the meaning of "one or more", "at least one", and "one or more than one".

As used in the specification and claims, the words "**comprising**" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, un-recited elements or method steps.

The term "**about**" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. In general, the terminology "about" is meant to designate a possible variation of up to 10%. Therefore, a variation of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10% of a value is included in the term "about".

In some aspects, the present description relates to a composition that may be useful for inducing or facilitating micturition in a subject in need thereof. As used herein, the term "**patient**" or "**subject**" means an animal including human. As used herein, the expression "**SCI patient**" or "**SCI subject**" means a subject that suffered a traumatic (e.g., car accident, fall, etc.) or non-traumatic (e.g., a degenerative disease such as multiple sclerosis (MS) or Parkinson's

disease (PD)) spinal cord injury, or other neurological diseases affecting the CNS or spinal cord that results in the subject having urinary retention problems. In some aspects, the SCI subject may be a patient with an irreversible loss of sensation and voluntary motor control below the level of injury. In some aspects, the SCI patient may be a paraplegic or quadriplegic patient, or an MS or PD patient. As used herein, the expression "**MS patient**" or "**MS subject**", or "**PD patient**" or "**PD subject**" refers to an SCI subject suffering from an affection to the spinal cord and diagnosed with multiple sclerosis or Parkinson's Disease.

In some aspects, compositions of the present description may comprise: (a) a 5-HT1A receptor agonist; (b) a 5 HT1A/7 receptor agonist; (c) a 5-HT2/3 receptor agonist; (d) a cholinesterase inhibitor; (e) an NMDA receptor agonist; (f) a noradrenaline/dopamine precursor; or (g) any combination of (a) to (f). In some embodiments, compositions defined herein may comprise a combination of at least two, at least three, at least four, at least five; between two and five, or between two and four of: (a) to (f). In some embodiments, the composition elicits acute micturition (voiding activity) in subjects having a spinal cord injury (SCI subject).

In some embodiments, one or more of (a) to (f) may be chosen from **Table 1**, or a pharmaceutically acceptable derivative of a compound listed In **Table 1**. In some embodiments, the agents of **Table 1** can be used alone or in combination with each other or with pharmaceutically acceptable derivatives thereof.

It is understood that when **sub-classes of agonists** are identified, it means that the agonist has greater affinity for the subclass of receptor mentioned than for the other receptors within that class. For example, a 5-HT2/3 receptor agonist has more affinity for serotonin receptor subtypes 2 and 3.

Table 1: Classes, sub-classes and representative agents

Class	Sub-class	Agent
5-HT (serotonin) receptor agonists	5-HT1A receptor agonist	Buspirone; Tandospirone; Cannabidiol; F-15,599; Flesinoxan; Gepirone; Ipsapirone; Quetiapine; Trazodone; Yohimbine; Indole alkaloid; Asenapine; Vortioxetine; Ziprasidone
	5 HT1A/7 receptor agonist	8-OH-DPAT; 5-CT (5-carboxamidotryptamine)
	5-HT2/3 receptor agonist	Quipazine; SR57227A; LSD; mescaline; psilocin; DMT; 2C-B; Lorcaserin; 2-Methyl-5-HT; BZP; RS-56812
Parasympathomimetic agents	Cholinesterase inhibitor	Neostigmine; Physostigmine; Pyridostigmine; Rivastigmine
Glutamate receptor agonists	NMDA receptor agonist	NMDA (N-methyl-D-aspartate); Aminocyclopropanecarboxylic acid; D-Cycloserine; cis-2,3-Piperidinedicarboxylic acid; L-aspartate; Quinolinate; Homocysterate; D-serine; ACPL; L-alanine; GLYX-13; 3,5-dibromo-L-phenylalanine
Noradrenaline/dopamine precursor (dopaminergic/adrenergic precursors)		L-DOPA (L-DOPA/carbidopa); Phenylalanine; Tyrosine; L-threo-3,4-dihydroxyphenylserine

In some aspects, the noradrenaline/dopamine precursor may be L-DOPA. L-DOPA is also known as levodopa, chemically known also as L-(-)-2-amino-3-(3,4-dihydroxyphenyl)propionic acid, 3,4-dihydroxyphenyl-L-alanine, or 3-hydroxy-L-thyrosine, which is an amino acid of natural origin. In a further aspect, L-DOPA may be combined with a decarboxylase inhibitor such as benserazide or carbidopa ("L-DOPA/carbidopa") (e.g., with a ratio of 4:1) to increase central nervous system availability of the drug upon systemic administration.

In some aspects, the composition may comprise one or more of buspirone, 8-OH-DPAT, L-DOPA/carbidopa, NMDA, quipazine, and neostigmine. In some aspects, the combination may comprise buspirone and 8-OH-DPAT.

In some aspects, the uses, methods, compositions and combinations may comprise a further therapeutic agent indicated for the treatment of spinal cord injuries, multiple sclerosis, or other neurological disorders where descending signaling pathways (from brain to spinal structures) may be impaired such as Parkinson's disease or aging associated also with similar urinary retention problems.

As used herein, the expression "**pharmaceutically acceptable derivative**" of a compound described herein refers to a pharmaceutically suitable compound that shares at least some level of structural and functional similarity to a compound of the present description. For example, a "pharmaceutically acceptable derivative of buspirone" refers to a compound having a core chemical structure that is similar to buspirone (e.g., is chemically synthesizable or derivable from buspirone), and is able to bind to the same molecular target or targets (i.e., 5-HT1A receptor) with a similar specificity as buspirone. Pharmaceutically acceptable derivatives may include any pharmaceutically acceptable salts, pro-drugs, metabolites, esters, ethers, hydrates, polymorphs, solvates, complexes, enantiomers or adducts of a compound described herein which, upon administration to a subject, is capable of providing (directly or indirectly) the parent compound.

In some aspects, compositions as defined herein may be used for acutely inducing or facilitating micturition in a subject (e.g., an SCI subject), for the manufacture of a medicament for same, or in a method for treating a subject having urinary retention. As used herein, "**urination**" or "**micturition**" refers to the process of disposing urine from the urinary bladder through the urethra to the outside of the body. Normal urination involves contraction of the bladder muscle (detrusor) and relaxation of the valve muscles (sphincters), enabling urine to pass through the urethra to the outside of the body. As used herein "**inducing or facilitating**" means an increase in micturition frequency and/or an increase in urine amount disposed in patients with urine retention problems. In some embodiments, the use and methods as described herein may be used to induce or facilitate daily micturition (e.g., once or twice daily). As used herein "**acutely inducing or facilitating**" means a rapid increase, within 30 minutes upon administration of a composition described herein, in micturition frequency and/or an increase in urine amount disposed in subjects with urine retention problems. In some aspects, the compositions, uses and methods of the present description can be used to induce or facilitate acute micturition (e.g., within 30 minutes of administration).

In some aspects, therapeutically effective amounts of the 5HT2/3 receptor agonist, 5HT1A receptor agonist, a 5-HT1A/7 receptor agonist, the noradrenaline/dopamine precursor, the NMDA receptor agonist, or the cholinesterase

inhibitor are used in the uses, methods, compositions and combinations described herein. The expression "**therapeutically effective amount**" refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought be a researcher or clinician. In some aspects, the therapeutically acceptable amount is the amount required to elicit or induce the increase urination or micturition in the patient or subject (e.g., acute micturition).

In some embodiments, the present description is intended to include all pharmaceutically acceptable ionized forms (e.g., salts) and solvates (e.g., hydrates) of the compounds, regardless of whether such ionized forms and solvates are specified, since it is well known in the art to administer pharmaceutical agents in an ionized or solvated form. It is also noted that, unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (e.g., enantiomers or diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers.

The present description also relates to pharmaceutically acceptable salts compounds recited herein. By the expression "**pharmaceutically acceptable salts**" are meant those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toleune p sulphonic, tartaric, acetic, trifluoroacetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene 2 sulphonic and benzenesulphonic acids. Salts derived from amino acids are also included (e.g. L-arginine, L-Lysine). Salts derived from appropriate bases include alkali metals (e.g. sodium, lithium, potassium) and alkaline earth metals (e.g. calcium, magnesium). With regards to pharmaceutically acceptable salts, see also the list of FDA approved commercially marketed salts listed in Table I of Berge et al., Pharmaceutical Salts, J. of Phar. Sci., vol. 66, no. 1, January 1977, pp. 1-19.

It will be appreciated by those skilled in the art that compounds can exist in different polymorphic forms. As known in the art, polymorphism is an ability of a compound to crystallize as more than one distinct crystalline or "**polymorphic**" species. A polymorph is a solid crystalline phase of a compound with at least two different arrangements or polymorphic forms of that compound molecule in the solid state. Polymorphic forms of any given compound are defined by the same chemical formula or composition and are as distinct in chemical structure as crystalline structures of two different chemical compounds.

It will be appreciated that the amount of compounds required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition for which treatment is required and the age and condition of the patient and will be ultimately at the discretion of the attendant physician.

The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day (e.g., one or more unitary doses). For example, the compositions as described herein may be a fixed-dose combination. In some embodiments, the compositions described herein may comprise between 1 and 500 mg of the compounds listed in **Table 1**, or pharmaceutically acceptable derivatives thereof. In view of the present description, persons of skill in the art will be able

to select the proper dosages of each compound to acutely trigger micturition, depending on a number of factors such as the potency or toxicity of the compound, the desired route of administration, and the age and/or weight of the subject. For example, compositions described herein for oral administration may comprise between 2.5 and 50 mg of a 5-HT1A receptor agonist (e.g., buspirone), or between 15 and 150 mg of a cholinesterase inhibitor (e.g., neostigmine).

While it is possible that, for use in therapy, the compounds may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical composition. In some embodiments, the present description thus further relates to a pharmaceutical combination or composition of the compounds as described herein or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In some embodiments, the compounds described herein may be prepared as dosage forms for once or twice daily administration. In some embodiments, dosage forms may be immediate release dosage forms that can be taken by a subject "on-demand" in order to acutely elicit micturition.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The compositions may, where appropriate, be conveniently presented in discrete dosage units (e.g., unitary dosages) and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired composition.

Pharmaceutical compositions suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients, such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of

sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds may be formulated as ointments, creams or lotions, or as a transdermal patch. Such transdermal patches may contain penetration enhancers such as linalool, carvacrol, thymol, citral, menthol and t-anethole. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Compositions suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid are for example presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds or combinations may be used as a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or non-aqueous base also comprising one more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation the compounds or combinations are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds or combinations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

As used herein, the expression "**an acceptable carrier**" or "**a pharmaceutically acceptable excipient or carrier**" means a vehicle for the combinations and compounds described herein that can be administered to a subject without adverse effects. Suitable carriers known in the art include, but are not limited to, gold particles, sterile water,

saline, glucose, dextrose, or buffered solutions. Carriers may include auxiliary agents including, but not limited to, diluents, stabilizers (e.g., sugars and amino acids), preservatives, wetting agents, emulsifying agents, pH buffering agents, viscosity enhancing additives, colors and the like.

Some aspects of the present description relate to combinations and compositions as described herein, wherein the compounds are used sequentially or simultaneously.

When the combination partners employed in the combinations as disclosed herein are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the package insert of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise

In some embodiments, the present description relates to a kit comprising compositions defined herein; and a suitable container.

EXAMPLES

EXAMPLE 1:

Incidence of micturition following drug administration i.p. in non-acclimated spinal cord-transected mice

1.1 MATERIALS AND METHODS

Animal model and surgical procedures

All experimental procedures were conducted in accordance with the Canadian Council for Animal Care (CCAC) guidelines and accepted by the Laval University Animal Care and Use Committee. Data obtained from mice (Charles River, Montreal, QC) initially weighing 30-40 g prior to surgery were analyzed in this example. Preoperative care included lactate-Ringer's solution (1 mL, administered subcutaneously (s.c.), analgesic (buprenorphine; 0.1 mg/kg, s.c., Schering-Plough, Pointe-Claire, QC), and antibiotic (Baytril™; 5 mg/kg, s.c., Bayer, Toronto, ON). Spinal transection at the low-thoracic level was performed under complete anesthesia with 2.5% isoflurane. The spinal cord was completely transected intervertebrally using microscissors (no. 15000-08, Fine Science Tools, North Vancouver, B.C.) inserted between the 9th and 10th thoracic vertebrae ("Th9/10", Guertin and Steuer, 2005). To ensure that complete transection (Tx) was achieved, the inner vertebral walls were explored and entirely scraped several times with scissor tips in order to disrupt any small fibres which had not been previously severed. Opened skin areas were sutured and animals were placed for a few hours on heating pads. Postoperative care included administration of lactate-Ringer's solution (2 x 1 mL/day, s.c.), buprenorphine (0.2 mg/kg/day, s.c.) and Baytril™ (5 mg/kg/day) for four consecutive days. Bladders were also emptied manually for four days or until a spontaneous return of some micturition. Animals were left in their cages with food and water *ad libitum*. Complete Tx was confirmed by 1) mainly flaccid hindlimbs and 2) post-mortem examination of the lesioned area using either coronal or longitudinal sections of the spinal cord stained with luxol blue

and cresyl violet. In **Fig. 1,** panel A shows a typical Th9/10 transection without staining, and panel B shows another luxol blue and cresyl violet-stained cord clearly showing complete transection at the site of lesion.

Drug administration and protocol

Tests with agents (drugs) administered separately by intraperitoneal injection (i.p.) were performed either at 7, 14, 21 or 28 days post-Tx. Drug selection was based upon known corresponding receptor family classes and subclasses in the spinal cord or other related cellular targets. For each compound, corresponding low and high doses were chosen based on binding affinity data available and evidence of central-mediated effects in the literature (see selected dose ranges below and in the Results section of this example).

Data collection and analysis

After drug administration, we assessed micturition activity as follows. Episodes of micturition (urine expulsion out-urethra) were assessed during a 30 min-period of observation. Incidence was calculated as the number of tested animals in which at least one episode of micturition was found. Volumes were assessed qualitatively on a scale of 5 in earlier experiments in male mice whereas volumes were weighed (grams) in subsequent studies in female mice.

Statistical analysis

Results were reported as percentages (incidences) of the total number of tested animals for each group in which at least one episode of micturition was found within 30 min post-administration.

1.2 RESULTS

Incidence of micturition-inducing effects:

Figure 2A (Figure 2 in provisional application) shows the effects of different classes of compounds (e.g., cathecolaminergic, monoaminergic, or peptidergic compounds) administered separately i.p. on the incidence of micturition elicited in 30 minutes. The groups in Fig. 2A are as follows: **(1)** quipazine; **(2)** L-DOPA/carbidopa; **(3)** NMDA; **(4)** clenbuterol; and **(5)** pilocarpine. Animals per group (drug) or subgroup (dose) = 8 spinal cord-transected male mice typically tested at 7-10 days post-Tx.

Figure 2A shows some drugs that were associated with micturition-inducing effects defined as incidences greater than 75-80% of the tested animals. Specifically, 250 and 62.5 mg/kg L-DOPA/carbidopa (dopaminergic/adrenergic precursor/decarboxylase inhibitor; Group 2), 25 mg/kg NMDA (glutamate receptor agonist; Group 3), and 5 mg/kg quipazine (5-HT2A receptor agonist; Group 1) administered individually elicited episodes of urination in at least 85% of the animals tested. **Fig. 2A** also shows that two (2) drugs were associated with a complete lack of urination at both low and high doses in Tx mice. Indeed, none of the animals treated with 0.5 and 2.5 mg/kg

clenbuterol (beta-2 adrenergic agonist; Group 4) or 0.25 mg/kg pilocarpine (muscarinic agonist; Group 5) displayed episodes of urination.

Figure 2B shows the results (% incidence of micturition) from further experiments in which drugs were administered separately i.p. to spinal cord-transected mice in different groups (8-10 spinal cord transected mice tested per group with drug administration occurring 7-28 days post-Tx). Specifically, we tested within physiological doses and compared the effects on incidence of: **(1)** 8-OH-DPAT; **(2)** buspirone; **(3)** DOI; **(4)** 7-OH-DPAT; **(5)** quipazine; **(6)** TFMPP; **(7)** L-DOPA/carbidopa; **(8)** clenbuterol; **(9)** clonidine; **(10)** moxonidine; **(11)** oxymetazoline; **(12)** NMDA; **(13)** A68930; **(14)** quipirole; **(15)** PD168077; **(16)** salbuterol; **(17)** TRH; **(18)** GR73632; **(19)** GR64349; **(20)** tizanidine; **(21)** midodrine; **(22)** SR57227A; **(23)** guanfacine; **(24)** methoxamine; **(25)** pilocarpine; **(26)** neostigmine; **(27)** physostigmine (n = 1); **(28)** AS19; and **(29)** H_2O (control). Dosages tested ranged generally between 0.1 and 5 mg/kg, except for neostigmine (0.00001-0.1 mg/kg), L-DOPA (25-100 mg/kg), carbidopa (5-25 mg/kg), and NMDA (10-75 mg/kg), for which either lower or higher doses have been shown to elicit centrally-mediated actions.

The results provided evidence that several types of ligands elicited acute (within minutes) micturition activities above control level (administration of water instead of ligands).

1.3 CONCLUSION

This earlier series of drug screening experiments has shown that various types of ligands elicited acute micturition activities above control level (water) – that is, incidence of micturition close to and beyond 75%. However, given that those earlier experiments were conducted in non-acclimated animals, this may explain why the incidence of micturition in the control groups (H_2O) was relatively high.

EXAMPLE 2:

Volume of micturition following drug administration in acclimated spinal cord-transected mice

2.1 MATERIALS AND METHODS

Animal model and surgical procedures

All experimental procedures were conducted in accordance with the CCAC guidelines and accepted by the Laval University Animal Care and Use Committee. Data obtained from 529 CD1 mice (Charles River, Montreal, QC), initially weighing 30-40 g prior to surgery, were analyzed in this study. All mice underwent acclimation (see section below). Preoperative care included lactate-Ringer's solution (1 mL, s.c.), analgesic (buprenorphine; 0.1 mg/kg, s.c., Schering-Plough, Pointe-Claire, QC), and antibiotic (Baytril™; 5 mg/kg, s.c., Bayer, Toronto, ON). Spinal transection at the low-thoracic level was performed under complete anesthesia with 2.5% isoflurane. The spinal cord was completely transected (Tx) intervertebrally using microscissors (no. 15000-08, Fine Science Tools, North Vancouver, B.C.) inserted between the 9th and 10th thoracic vertebrae ("Th9/10", Guertin and Steuer, 2005). To ensure that complete transection

was achieved, the inner vertebral walls were explored and entirely scraped several times with scissor tips in order to disrupt any small fibres which had not been previously severed. Opened skin areas were sutured and animals were placed for a few hours on heating pads. Postoperative care included administration of lactate-Ringer's solution (2 x 1 mL/day, s.c.), buprenorphine (0.2 mg/kg/day, s.c.) and Baytril™ (5 mg/kg/day) for four consecutive days. Bladders were emptied manually until the day of testing. Animals were left in their cage with food and water *ad libitum*. Complete Tx was confirmed by 1) mainly flaccid hindlimbs and 2) post-mortem examination of the lesioned area using either coronal or longitudinal sections of the spinal cord stained with luxol blue and cresyl violet (e.g., see **Fig. 1**).

Acclimation

Upon arrival at the animal care facilities, animals were housed in groups of 3 or 4 mice per cage, with freely access to food and water during 7 days for general acclimation to the new housing environment. The last 3 days of that first week were used also for a more specific acclimation procedure – acclimation to the laboratory where experiments will be conducted. During these 3 days, they were placed as small groups (animals of a same cage) during 30 min per day in a circular Plexiglas™ arena (diameter of 60 cm), which would we used to observe the animals following drug administration. Generally, the results showed that during the first 15 min, most mice were particularly active at exploring that new environment. Then, exploration and corresponding locomotor activity decreased progressively for the remaining 15 min. Towards the third day, complete immobility and grooming was even found during the first 15 min suggesting that less stress was experienced by the animals when placed in the Plexiglas™ arena. On the day of testing, each group was acclimated one last time for 10 minutes in the Plexiglas™ arena prior to administrations. Then each animal was tested separately. Following administration of sterile water (control) or a drug, the animal was examined for 30 min during which urine was collected immediately upon expulsion. Generally, several episodes of voiding were found within that 30 min-period of observation.

Drug administration and protocol

Experiments in which drugs were administered separately were performed typically between 7 and 28 days post-Tx, unless otherwise indicated. For each drug, corresponding low and high doses were chosen based on binding affinity data available or evidence of central-mediated effects in the literature. Animal groups generally consisted generally of at least 8 spinal cord-transected (Tx) mice per group (drug or drug combination) or subgroup (dose). Drug solutions were prepared each day of experiments a few hours before testing using sterile water. Parenteral or oral administrations consisted of a bolus injection. For subcutaneous administrations, 0.5-1 mL of solution was injected in the back area of the animal. For oral administrations, 0.2 mL of solution was delivered by gavage using a bended needle for that purpose.

Data collection

After drug administration, we assessed micturition activity as follows. Episodes of micturition (urine expulsed from the urethra) were assessed during a 30 min-bout of observation. Incidence (expressed as a percentage) was calculated as the number of tested animals in which at least one episode of micturition was found. Amounts (volumes) of urine expulsed were determined by placing the animals on pre-weighed Whatman™ filter paper and calculating the weight gain of the filter paper following the 30 min observation period (i.e., soaked filter paper – dry filter paper = collected urine amount in mg).

Statistical analysis

Results were reported either as percentages (incidences) or as amounts of urine (average amount of urine expulsed in mg per animal). Two-way ANOVA followed by a Bonferroni post-test, using GraphPad Prism™ 5.0 software. Quantitative results were expressed as mean ± SEM. P values < 0.05 were considered statistically significant.

2.2 RESULTS

We initially established baseline levels corresponding to the amounts of urine expulsed by Tx and non-Tx mice receiving water (control group) via different routes of administration. The left-end bars in **Figures 3-5**, show the effects of s.c. administration of water (control) to Tx mice. In **Fig. 4**, Tx mice expulsed an average of 13.6 ± 7.2 mg of urine per animal (male and female; n = 20) following water administration s.c. Comparable observations were made in Tx animals receiving water per os (oral gavage – average of 12.9 ± 11.2 mg of urine per animal; n = 10, see **Figure 5**, left-end bar). No significant difference ($p > 0.05$) was found between control groups receiving water via s.c. or p.o. Non-Tx mice receiving either 1 or 0.5 mL s.c. expressed an average of 8.6 ± 5.5 mg of urine per animal within 30 min post-administration (male and female; n = 20; data not shown).

Figure 3 (Fig. 3 in provisional application) shows that quipazine, buspirone, 8-OH-DPAT, and neostigmine administered s.c. 7, 14, 21 or 28 days post-Tx elicited significant acute voiding-inducing effects. Volumes of urine ranging between 90 mg and 120 mg were measured within 30 minutes post-administration, which in all cases were significantly greater ($p < 0.05$; "*") than control (administration of 0.5 mL water). Specifically, animals receiving water, quipazine, buspirone, 8-OH-DPAT or neostigmine expressed respectively an average of 13.3 ± 5.2 mg (n = 10), 94.7 ± 26.9 mg (n = 10), 106 ± 36.7 mg (n = 10), 99.5 ± 35.5 mg (n = 22) and 82.8 ± 44.8 mg (n = 10) of urine per animal.

Figure 4 shows the effects in Tx mice of various subtypes of serotonergic (5-HT) receptor agonists (s.c. administration). Mice generally received 0.5 mL s.c. of AS19 (5-HT7 receptor agonist; 2.5 mg/kg; n = 5), SR57227 (5-HT3 receptor agonist; 3 mg/kg; n = 10), quipazine (5-HT2/3 receptor agonist; 1-5 mg/kg; n = 32), buspirone (5-HT1 receptor agonist; 1-3 mg/kg; n = 19), or 8-OH-DPAT (5-HT1A/7 receptor agonist; 0.5-5 mg/kg; n = 16). Within 30 min post administration, an average of 13.6 ± 7.2 mg (control, water), 0 mg, 8.8 ± 4.0 mg, 63.0 ± 18.6 mg, 110.0 ± 27.5 mg, and 100.4 ± 13.7 mg of urine per animal, respectively, was expulsed. Significant differences ($p < 0.05$) were found between the last three groups (quipazine, buspirone, and 8-OH-DPAT) vs. control. Non-significant difference was found

between buspirone-treated animals and 8-OH-DPAT-treated ones. In contrast to the results presented in **Figure 3**, some mice having empty bladders prior to the drug administration (verified by rolling/manual palpation of the bladder) were excluded from the results presented in **Figure 4**.

2.3 CONCLUSION

Results from this series of experiments showed that expulsion of significant amounts of urine can be induced pharmacologically within minutes upon single administration s.c. or p.o. of some specific families of ligands, such as some 5-HT1A receptor agonists, 5-HT1A/7 receptor agonists, 5-HT2/3 receptor agonists, or cholinesterase inhibitors.

EXAMPLE 3:

Effects of different doses of buspirone or 8-OH-DPAT administered separately s.c. or p.o. on amount of urine expulsed in spinal cord-transected mice 30 min post-administration

3.1 PROTOCOL AND RESULTS

Acclimated mice were spinal cord transected and administered buspirone either subcutaneously (s.c.) or orally (p.o.) and evaluated for micturition within 30 min post-administration, as generally described in **Example 2.1**.

Figure 5 shows the effects of various doses of buspirone administered s.c. to Tx mice. Mice received 0.5 mL s.c. of 1 mg/kg (n = 9) or 3 mg/kg (n = 7) buspirone (5-HT1A agonist) 1 week post-Tx. Within 30 min post administration, 105.9 mg and 114.1 mg of urine were expulsed, respectively. No significant difference ($p > 0.05$) between both groups treated with buspirone was found.

Figure 6 shows the effects of various doses of buspirone administered by oral gavage (per os – p.o.) in Tx mice. Mice received 0.2 mL orally of 2.5 mg/kg (n = 7) or 10 mg/kg (n = 9) buspirone (5-HT1A receptor agonist) or water 1 week post-Tx. Within 30 min post administration, averages of 54.8 mg ± 17.7 mg, 18.9 ± 19.8 mg, and 12.9 ± 11.2 of urine per animal, respectively, were expressed. Significant difference ($p < 0.05$) between the 2.5 mg/kg group and the other groups was found. Note that only mice that displayed at least some urination post-treatment were considered, given that these experiments were not accompanied of pre-assessment of urine retention (UR, potential for some false-negative data).

Figure 7 shows the effects of various doses of 8-OH-DPAT administered s.c. to Tx mice. Mice received 0.5 mL s.c. of 0.5 mg/kg (n = 2), 1 mg/kg (n = 10) or 5 mg/kg (n = 4) 8-OHDPAT (5-HT1A/7 agonist) 1-4 weeks post-Tx. Within 30 min post administration, averages of 97.5 ± 10.5 mg, 140.7 ± 43.5 mg, and 95.1 ± 28.9 mg of urine per animal, respectively, were expressed. No significant difference ($p > 0.05$) between 8-OH-DPAT-treated groups was found. However, significant differences with control (H_2O) were clearly induced.

Figure 8 shows the effects of 8-OH-DPAT administered by oral gavage (per os – p.o.) in Tx mice. Mice received 0.2 mL orally of 1 mg/kg (n = 8) 8-OH-DPAT (5-HT1A/7 receptor agonist) or water (n = 20) between 1 and 5

weeks post-Tx. Within 30 min post administration, averages of 56.1 ± 15.4 mg and 12.9 ± 11.2 of urine per animal, respectively, were expressed. Significant difference ($p < 0.05$) between both groups was found. Note that only mice that displayed at least some urination post-treatment were considered given that these experiments were not accompanied of pre-assessment of UR (potential for some false-negative data).

3.2 CONCLUSION

Results from this series of experiments provided evidence that some dose-dependent effects can be found. In turn, this suggests that micturition inducing effects may reach a plateau level independently when monotherapies are used.

EXAMPLE 4:

Effects of drug combinations administered s.c. or p.o. on amount of urine expulsed in spinal cord-transected mice 30 min post-administration

4.1 PROTOCOL AND RESULTS

Acclimated mice were spinal cord transected and administered different combinations of drugs either subcutaneously (s.c.) or orally (p.o.) and evaluated for micturition within 30 min post-administration, as generally described in **Example 2.1**.

Figure 9 shows the effects of s.c. administration of combinations of 8-OH-DPAT and buspirone in Tx mice. Mice received: (1) water (n = 20); (2) 0.5 mg/kg 8-OH-DPAT + 1 mg/kg buspirone (n = 3); or (3) 1 mg/kg 8-OH-DPAT + 1 mg/kg buspirone (n = 15) between 1 and 3 weeks post-Tx. Within 30 min post administration, averages of 13.6 ± 7.2 mg, 67.4 ± 53.8 mg, and 196.4 ± 72.1 mg of urine per animal, respectively, were expressed. Significant difference ($p < 0.05$) between the last group (1 mg each of 8-OH-DPAT and buspirone) vs control (H_2O) was found. Note that only mice that displayed at least some urination post-treatment were considered, given that these experiments were not accompanied of pre-assessment of UR (potential for some false-negative data).

Figure 10 shows the effects of combinations of 8-OH-DPAT and buspirone administered by oral gavage (per os – p.o.) in Tx mice. Mice received 0.2 mL orally of: (1) water (n = 20); (2) 1 mg/kg 8-OH-DPAT + 2.5 mg/kg buspirone (n = 6); (3) 5-10 mg/kg 8-OH-DPAT + 10-20 mg/kg buspirone (n = 3); or (4) 20 mg/kg 8-OH-DPAT + 40 mg/kg buspirone (n = 1) between 3 and 4 weeks post-Tx. Within 30 min post administration, averages of 12.9 ± 11.2 mg, 142.6 ± 33.9 mg, 213.6 ± 20.2 mg, 51.3 mg of urine per animal, respectively, were expressed. Significant differences ($p < 0.05$) between most groups vs control (H_2O) was found. Note that only mice that displayed at least some urination post-treatment were considered, given that these experiments were not accompanied of pre-assessment of UR (potential for some false-negative data).

Figure 11 shows the effects in Tx mice of other drug combinations delivered via s.c. administration. Mice received 0.5 mL s.c. of the drug combinations described in **Table 2** at between 1 and 5 weeks post-Tx. Significant difference ($p < 0.05$) between group number 5 and control (H_2O) was found.

Table 2: Drug combinations tested in Figure 11

Group in Fig. 11	Compound administered s.c.	Dose	Number of mice (n)	Average amount of urine expressed per Tx animal
1	Water (control)	0.5-1 mL	20	13.6 ± 7.2
2	Clenbuterol	0.5-2.5 mg/kg	20	24.7 ± 8.1 mg urine/animal
	Quipazine	1-5 mg/kg		
	GR64349	2.5-0.5 mg/kg		
3	8-OH-DPAT	0.5-1 mg/kg	15	43.7 ± 28.9 mg urine/animal
	SR57227	1.5-3 mg/kg		
	Quipazine	2.5-5 mg/kg		
4	8-OH-DPAT	mg/kg	10	26.8 ± 26.8 mg urine/animal
	Quipazine	mg/kg		
	SR57227	mg/kg		
	L-DOPA/carbidopa	50/12.5 mg/kg		
5	Clenbuterol	2.5 mg/kg	10	121.1 ± 46.4 mg urine/animal
	Quipazine	5 mg/kg		
	8-OH-DPAT	1 mg/kg		
6	Clenbuterol	2.5 mg/kg	10	0.6 ± 0.6 mg urine/animal
	8-OH-DPAT	1 mg/kg		
7	Neostigmine	0.01-0.1 µg/kg	10	27.9 ± 6.3 mg urine/animal
	8-OH-DPAT	1 mg/kg		
8	Neostigmine	0.01-0.1 µg/kg	23	42.0 ±19.4 mg urine/animal
	Buspirone	1-3 mg/kg		

4.2 CONCLUSION

Results from this series of experiments provided evidence showing that some drug combinations may induce significantly higher amounts of micturition as compared to individual drugs administered as monotherapies.

Although the present invention has been described hereinabove by way of specific embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims. The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole. The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

CLAIMS:

1. A composition comprising:
   (a) a 5-HT1A receptor agonist;
   (b) a 5-HT1A/7 receptor agonist;
   (c) a 5-HT2/3 receptor agonist;
   (d) a cholinesterase inhibitor;
   (e) an NMDA receptor agonist;
   (f) a noradrenaline/dopamine precursor; or
   (g) any combination of (a) to (f),

and optionally a pharmaceutically acceptable excipient or carrier, for inducing or facilitating micturition in a subject.

2. The composition of claim 1, wherein said composition comprises at least two, at least three, or at least four of (a) to (f).

3. The composition of claim 1 or 2, wherein said composition comprises a 5-HT1A receptor agonist, a 5-HT1A/7 receptor agonist, or both a 5-HT1A receptor agonist and a 5-HT1A/7 receptor agonist.

4. The composition of any one of claims 1 to 3, wherein said 5-HT1A receptor agonist is: (1) buspirone; (2) tandospirone; (3) cannabidiol; (4) F-15,599; (5) flesinoxan; (6) gepirone; (7) ipsapirone; (8) quetiapine; (9) trazodone; (10) yohimbine; (11) indole alkaloid; (12) asenapine; (13) vortioxetine; (14) ziprasidone; (15) a pharmaceutically acceptable derivative of any one of (1)-(14); or (16) any combination of (1)-(15).

5. The composition of any one of claims 1 to 4, wherein said 5-HT1A receptor agonist is buspirone, or a pharmaceutically acceptable derivative thereof.

6. The composition of any one of claims 1 to 5, wherein said 5-HT1A/7 receptor agonist is: (1) 8-OH-DPAT; (2) 5-CT; (3) a pharmaceutically acceptable derivative of (1) or (2); or (4) any combination of (1)-(3).

7. The composition of any one of claims 1 to 6, wherein said 5-HT1A/7 receptor agonist is 8-OH-DPAT, or a pharmaceutically acceptable derivative thereof.

8. The composition of any one of claims 1 to 7, wherein said composition comprises a 5-HT2/3 receptor agonist.

9. The composition of any one of claims 1 to 8, wherein said 5-HT2/3 receptor agonist is: (1) quipazine; (2) SR57227A; (3) LSD; (4) mescaline; (5) psilocin; (6) DMT; (7) 2C-B; (8) lorcaserin; (9) 2-methyl-5-HT; (10) BZP; (11) RS-56812; (12) a pharmaceutically acceptable derivative of any one of (1)-(11); or (13) any combination of (1)-(12).

10. The composition of any one of claims 1 to 9, wherein said 5-HT2/3 receptor agonist is quipazine, or a pharmaceutically acceptable derivative thereof.

11. The composition of any one of claims 1 to 10, wherein said composition comprises a cholinesterase inhibitor.

12. The composition of any one of claims 1 to 11, wherein said cholinesterase inhibitor is: (1) neostigmine; (2) physostigmine; (3) pyridostigmine; (4) rivastigmine; (5) any derivative of (1) to (4); or (6) any combination of (1)-(5).

13. The composition of any one of claims 1 to 12, wherein said cholinesterase inhibitor is neostigmine or a pharmaceutically acceptable derivative thereof.

14. The composition of any one of claims 1 to 13, wherein said composition comprises an NMDA receptor agonist.

15. The composition of any one of claims 1 to 14, wherein said NMDA receptor agonist is: (1) N-methyl-D-aspartate (NMDA); (2) aminocyclopropanecarboxylic acid; (3) D-cycloserine; (4) cis-2,3-piperidinedicarboxylic acid; (5) L-aspartate; (6) quinolinate; (7) homocysterate; (8) D-serine; (9) ACPL; (10) L-alanine; (11) GLYX-13; (12) 3,5-dibromo-L-phenylalanine; (13) any pharmaceutically acceptable derivative of (1) to (12); or (14) any combination of (1)-(13).

16. The composition of any one of claims 1 to 15, wherein said NMDA receptor agonist is NMDA.

17. The composition of any one of claims 1 to 16, wherein said composition comprises a noradrenaline/dopamine precursor, or a noradrenaline/dopamine precursor and a decarboxylase inhibitor.

18. The composition of any one of claims 1 to 17, wherein said noradrenaline/dopamine precursor is: (1) L-DOPA or L-DOPA/carbidopa; (2) phenylalanine; (3) tyrosine; (4) L-threo-3,4-dihydroxyphenylserine; (5) any pharmaceutically acceptable derivative of (1) to (4); or (6) any combination of (1)-(5).

19. The composition of any one of claims 1 to 18, wherein said composition comprises 8-OH-DPAT or a pharmaceutically acceptable derivative thereof, and buspirone or a pharmaceutically acceptable derivative thereof.

20. The composition of any one of claims 1 to 19, wherein said composition is for oral administration and comprises 2.5 to 50 mg of buspirone, and/or 5 to 150 mg of neostigmine.

21. Use of the composition as defined in any one of claims 1 to 20 for acutely inducing or facilitating micturition in a subject.

22. Use of the composition as defined in any one of claims 1 to 20 for the manufacture of a medicament for acutely inducing or facilitating micturition in a subject.

23. Use of:

(a) a 5-HT1A receptor agonist;
(b) a 5-HT1A/7 receptor agonist;
(c) a 5-HT2/3 receptor agonist;
(d) a cholinesterase inhibitor;
(e) an NMDA receptor agonist;
(f) a noradrenaline/dopamine precursor; or
(g) any combination of (a) to (f),

for inducing or facilitating micturition in a subject in need thereof.

24. The use of claim 27, wherein:

(a) said 5-HT1A receptor agonist is as defined in claim 4 or 5;
(b) said 5-HT1A/7 receptor agonist is as defined in claim 6 or 7;
(c) said 5-HT2/3 receptor agonist is as defined in claim 9 or 10;
(d) said cholinesterase inhibitor is as defined in claim 12 or 13;
(e) said NMDA receptor agonist is as defined in claim 15 or 16; or
(f) said noradrenaline/dopamine precursor is as defined in claim 18 or 19.

25. The use of claim 23 or 24, for inducing or facilitating acute micturition in a subject in need thereof.

26. The composition or use of any one of claims 1 to 25, wherein said subject suffers from urinary retention.

27. The composition or use of any one of claims 1 to 26, wherein said subject is a spinal cord injury (SCI) subject.

28. The composition of claim 27, wherein said SCI subject is a multiple sclerosis (MS) or Parkinson's disease (PD) subject.

29. The composition or use of any one of claims 1 to 28, wherein said composition is for administration by a route which is: oral; parenteral; or sublingual.

30. The composition or use of any one of claims 1 to 29, wherein said composition is for daily administration to said subject.

31. A method for inducing or facilitating acute micturition in a subject, said method comprising administering to said subject the composition as defined in any one of claims 1 to 20.

32. A kit comprising the composition as defined in any one of claims 1 to 20; and a suitable container.

Figure 1

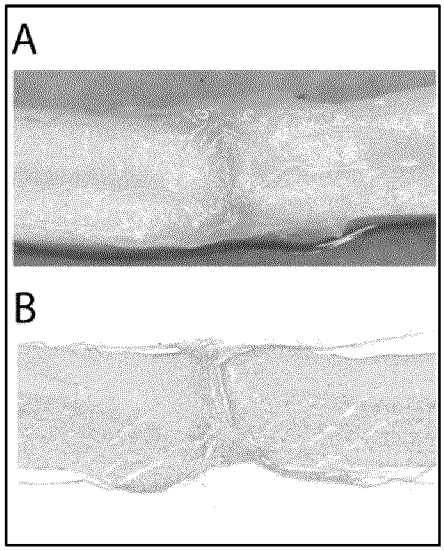


Figure 2A

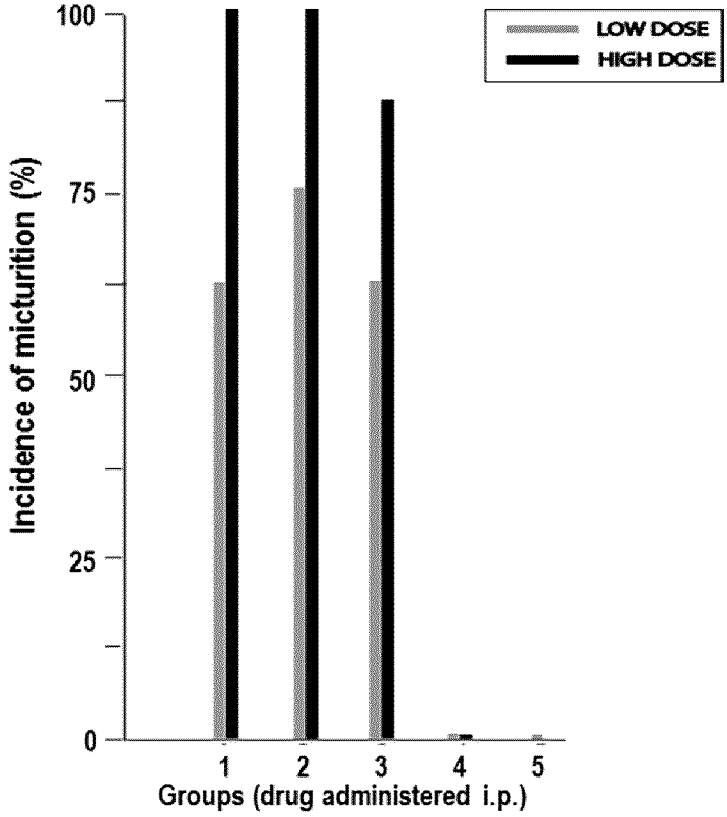


Figure 2B

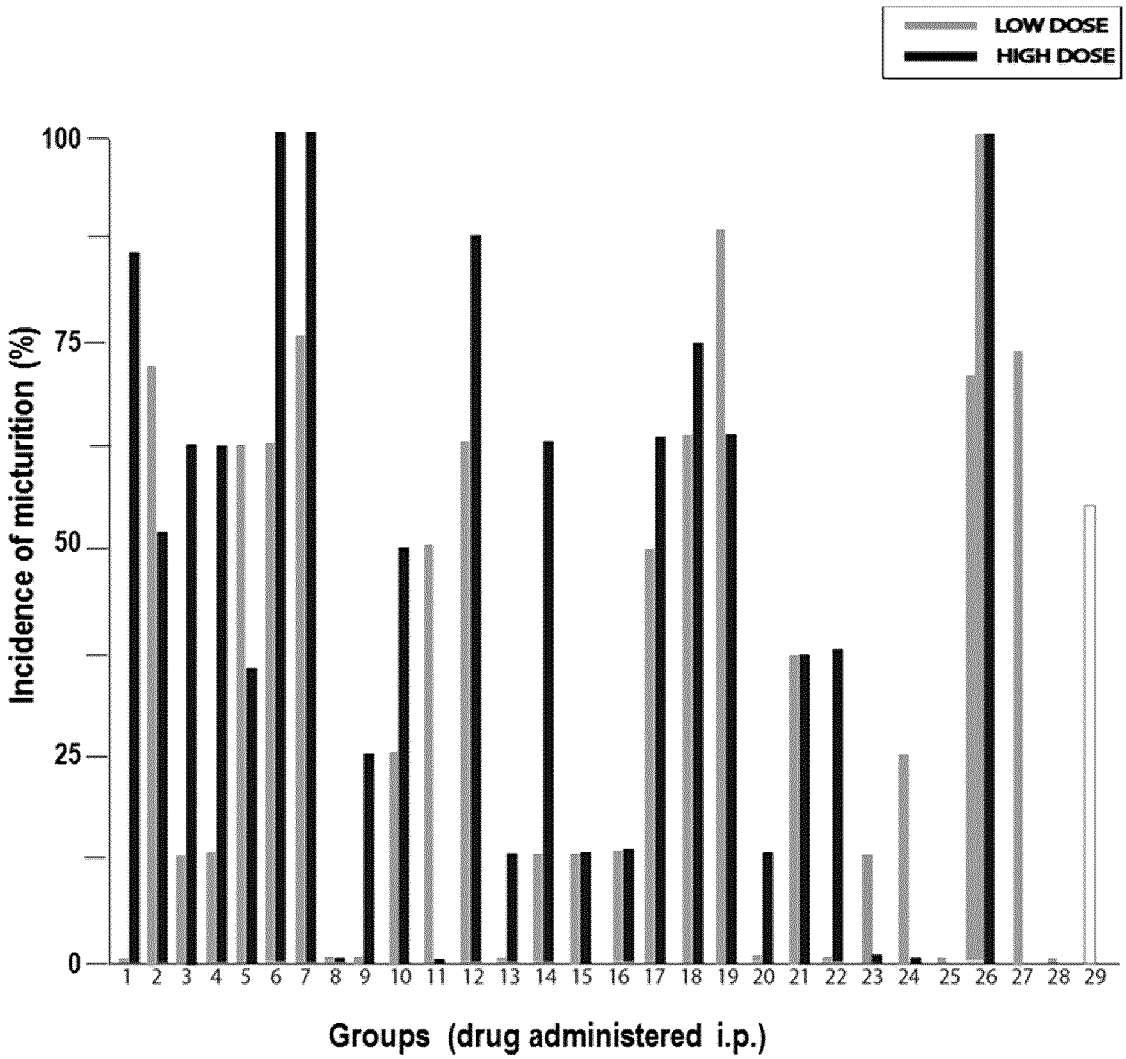

LOW DOSE
HIGH DOSE
Incidence of micturition (%)
100
75
50
25
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Groups (drug administered i.p.)

Figure 3

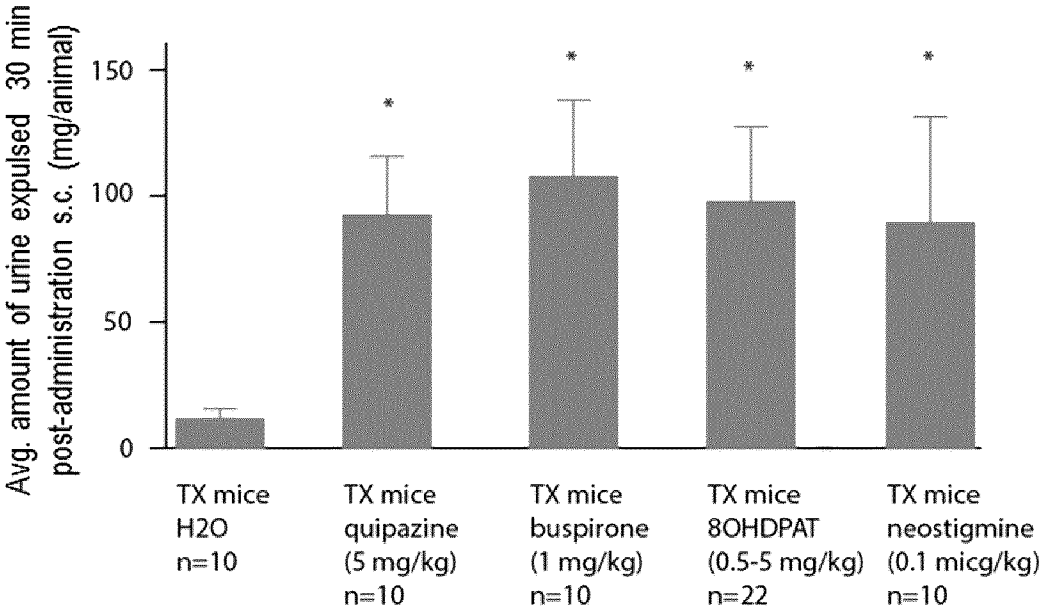


Figure 4

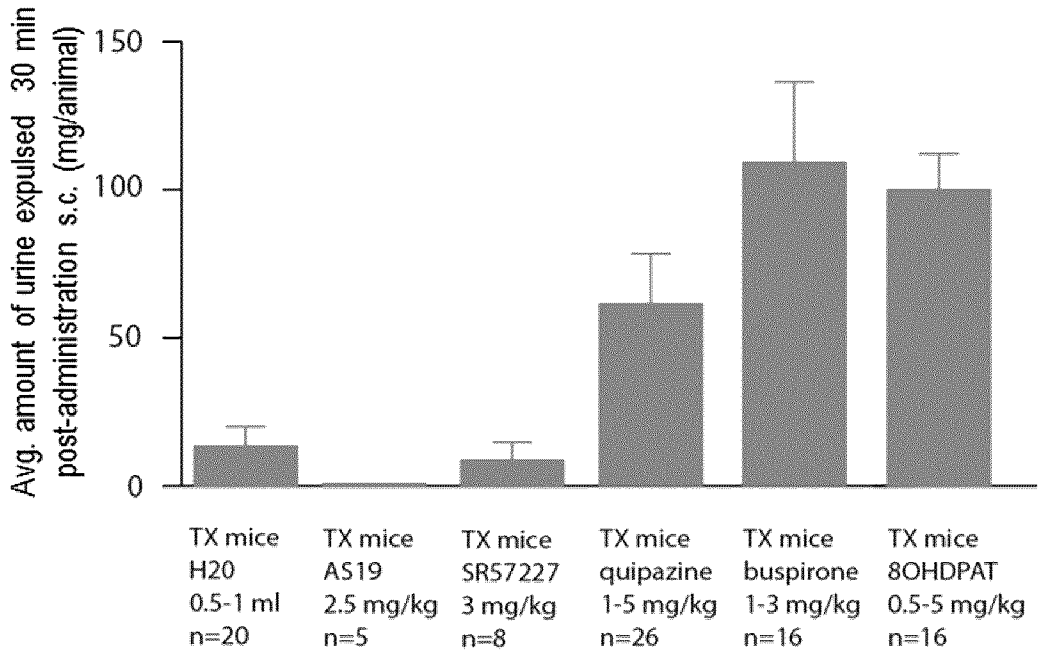


Figure 5

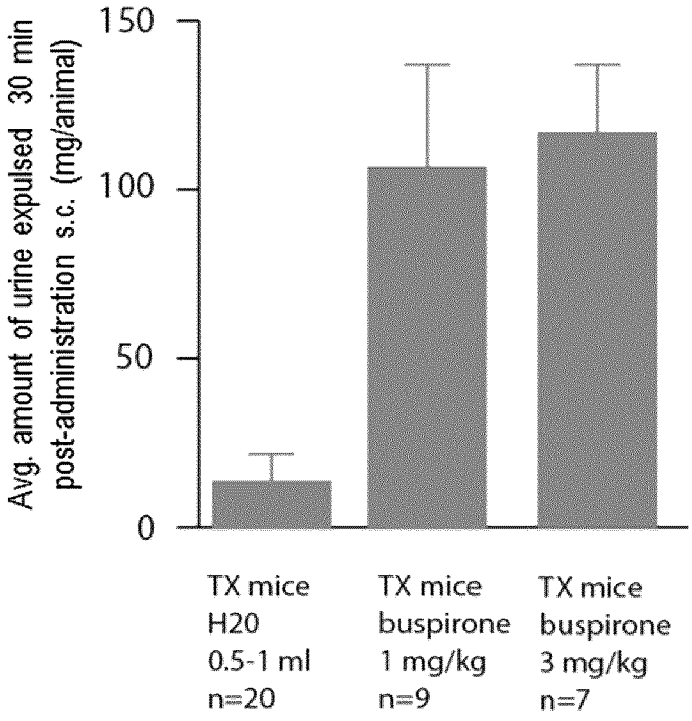


Figure 6

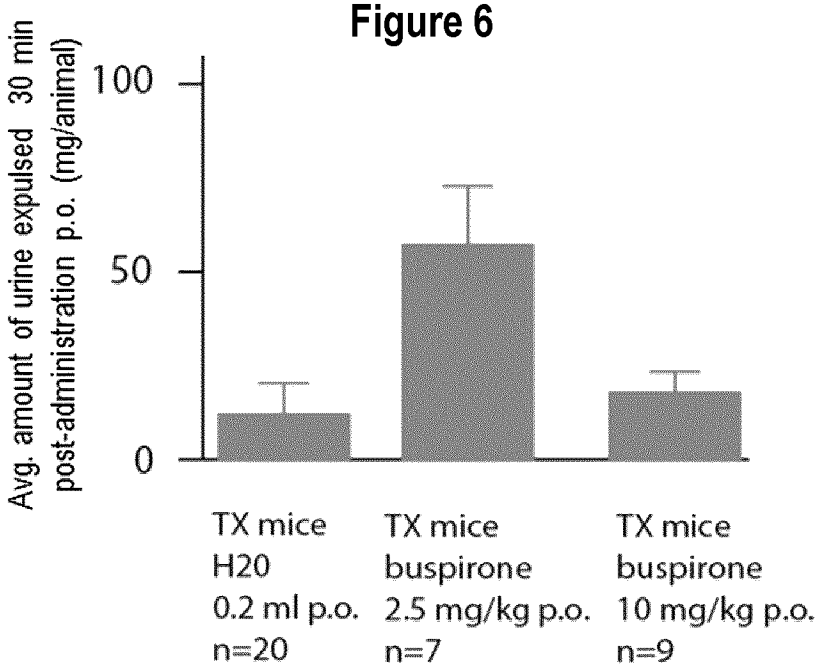


Figure 7

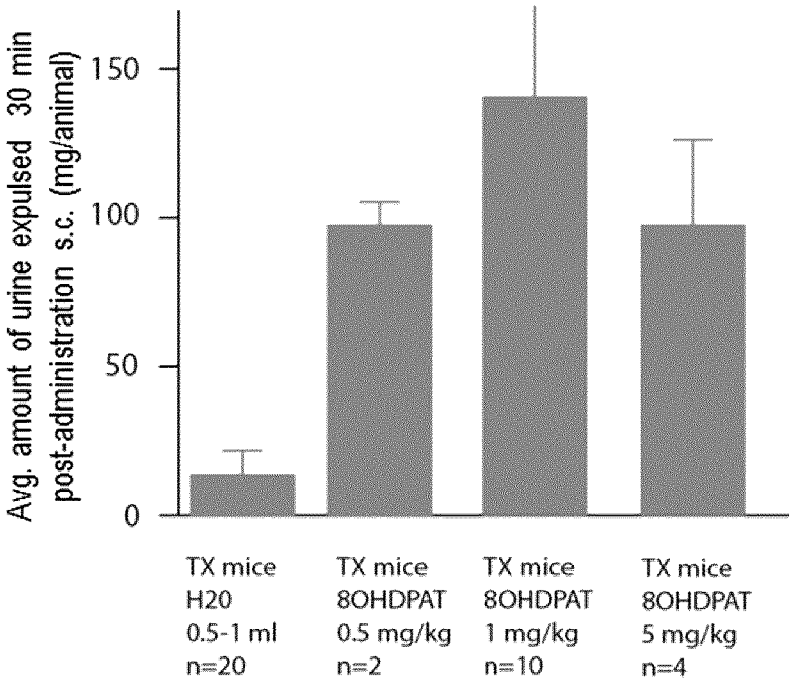


Figure 8

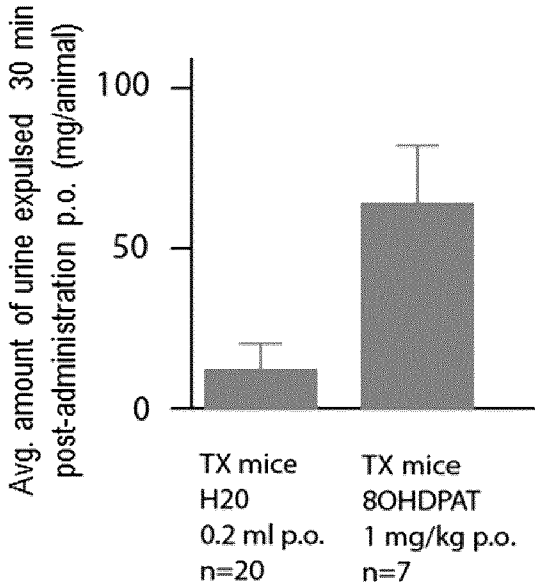


Figure 9

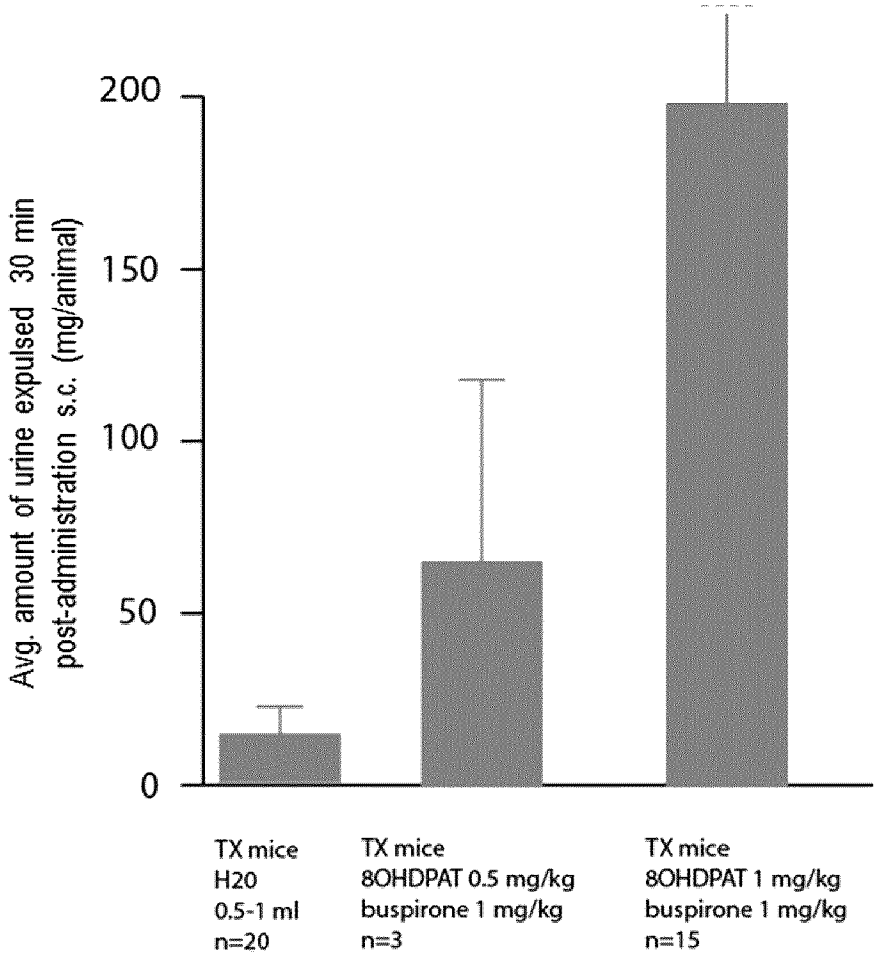

Avg. amount of urine expulsed 30 min post-administration s.c. (mg/animal)
200
150
100
50
0
TX mice
H20
0.5-1 ml
n=20
TX mice
8OHDPAT 0.5 mg/kg
buspirone 1 mg/kg
n=3
TX mice
8OHDPAT 1 mg/kg
buspirone 1 mg/kg
n=15

Figure 10

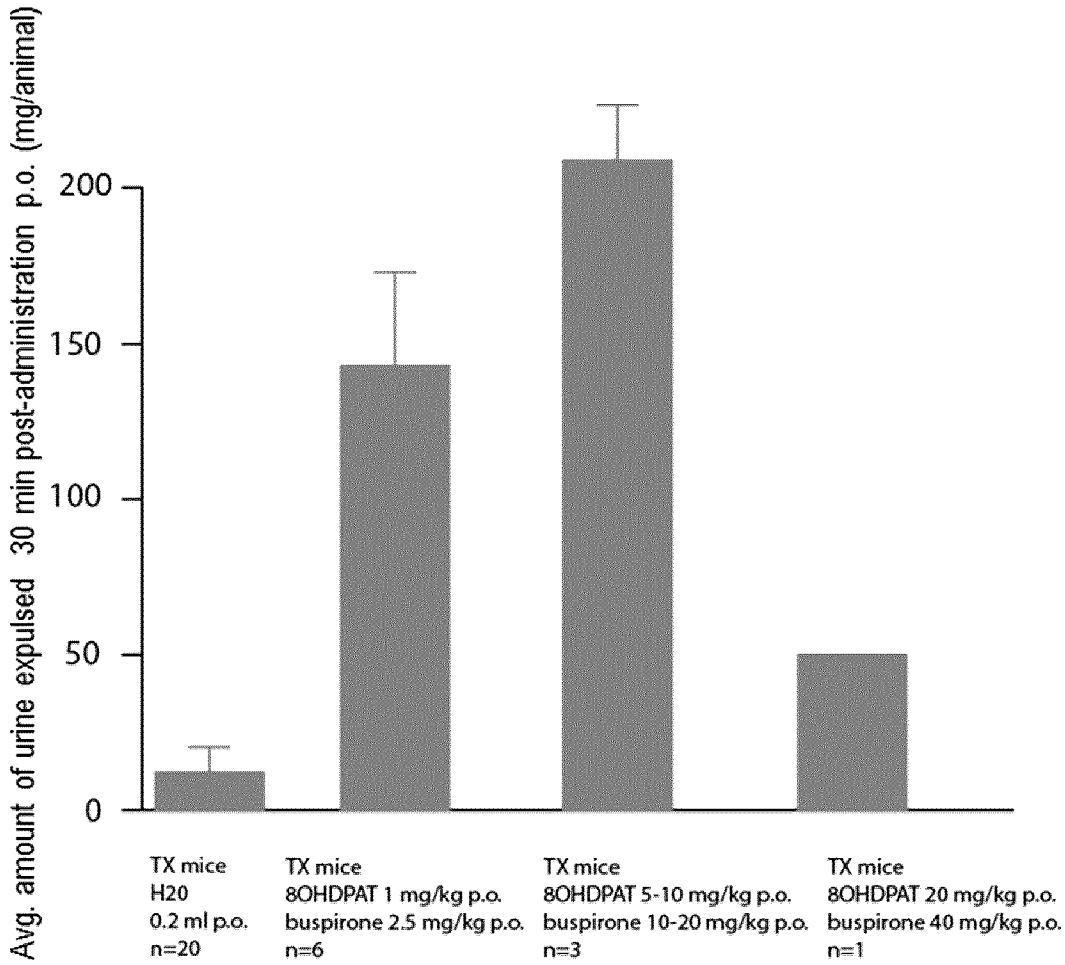
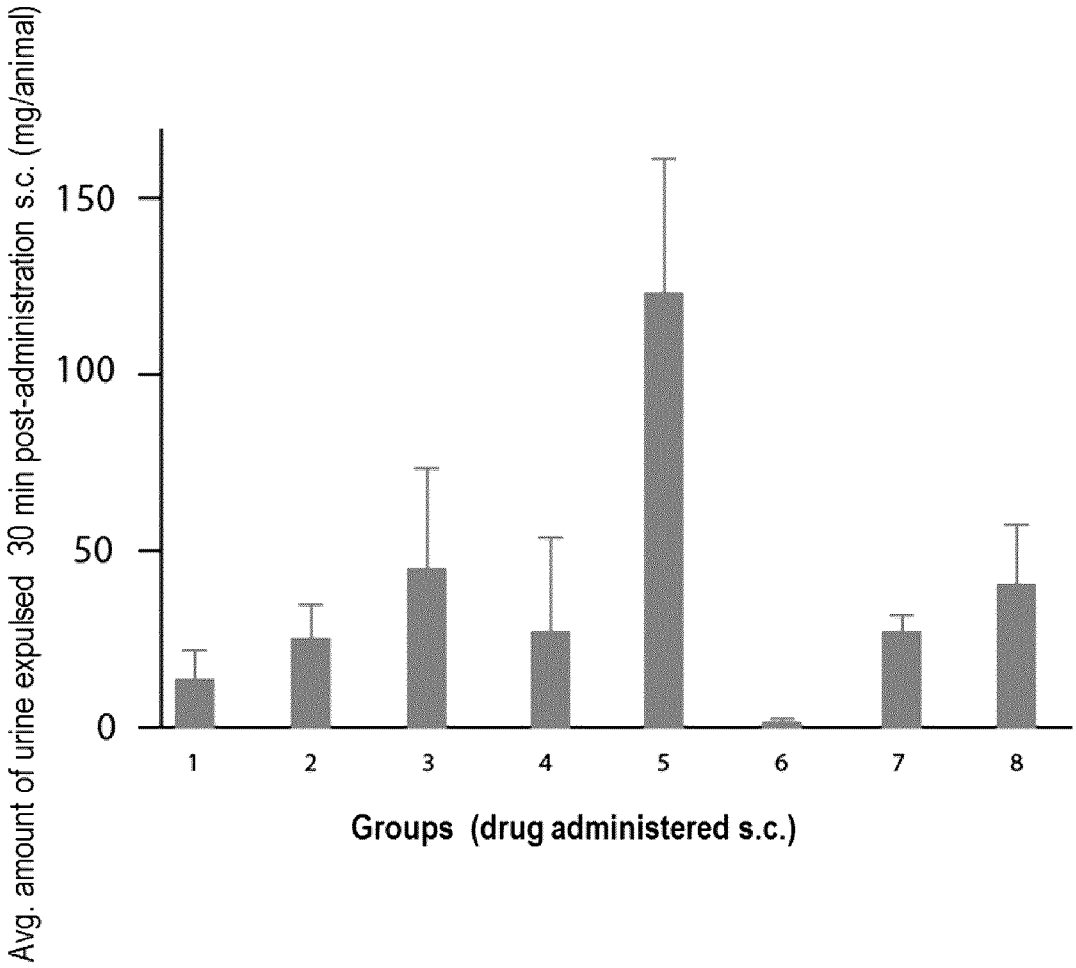

Avg. amount of urine expulsed 30 min post-administration p.o. (mg/animal)
200
150
100
50
0
TX mice
H20
0.2 ml p.o.
n=20
TX mice
8OHDPAT 1 mg/kg p.o.
buspirone 2.5 mg/kg p.o.
n=6
TX mice
8OHDPAT 5-10 mg/kg p.o.
buspirone 10-20 mg/kg p.o.
n=3
TX mice
8OHDPAT 20 mg/kg p.o.
buspirone 40 mg/kg p.o.
n=1

Figure 11


Avg. amount of urine expulsed 30 min post-administration s.c. (mg/animal)
150
100
50
0
1
2
3
4
5
6
7
8
Groups (drug administered s.c.)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2015/050146

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/506*** (2006.01), ***A61K 31/135*** (2006.01), ***A61K 31/198*** (2006.01), ***A61K 31/27*** (2006.01), ***A61K 31/47*** (2006.01), ***A61P 25/00*** (2006.01) (more IPCs on the last page)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: ***A61K 31/*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

QUESTEL (FAMPAT: Inventor search; micturition, voiding, uresis, emiction, urination, tinkling ,peeing, weeing, pissing, and compound search of Table 1)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2,654,934 A1 (CROCI et al) 31 May 1991 (31-05-1991) See the whole document.	1, 3-18, 20, 26-30, 32
X	WO 01/34124 A2 (RICHTER et al) 17 May 2001 (17-05-2001) See the whole document.	1, 3-18, 26-30, 32
X	WO 2005/107473 A2 (FARRUGIA) 17 November 2005 (17-11-2005) See the whole document.	1, 3-18, 26-30, 32
X	WO 2004/034963 A2 (IENI et al) 29 April 2004 (29-04-2004) See the whole document.	1, 3-18, 20, 26-30, 32
X	US 2004/0157926 A1 (HERESCO-LEVY et al) 12 August 2004 (12-08-2004) See the whole document.	1, 3-18, 26-30, 32

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search 08 May 2015 (08-05-2015)	Date of mailing of the international search report 25 May 2015 (25-05-2015)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Lu Jiang (819) 934-6738

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 253,490 A1 (DEMPSKI et al) 20 January 1988 (20-01-1988) See the whole document.	1, 3-18, 26-30, 32

C07C 215/64 (2006.01) , *C07C 229/36* (2006.01) , *C07C 271/44* (2006.01) , *C07D 215/38* (2006.01) , *C07D 401/12* (2006.01)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2015/050146

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claim Nos.: 31
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 31 is directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to search under Rule 39.1(iv) of the PCT. However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 31.

2. ☑ Claim Nos.: 1-23, 25-32
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant=s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

"5-HT1A receptor agonist", "5-HT1A/7 receptor agonist", "5-HT2/3 receptor agonist", "cholinesterase inhibitor", "NMDA receptor agonist" and "noradrenaline/dopamine precursor" encompass all compounds having these common functions or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). The expression does not define any particular kind of compound(s) but rather the effect that the desired compound(s) should possess. Again, this lack of clarity in the present application renders a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds disclosed in Table 1 of the description on page 7.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2015/050146

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
FR2654934A1	31 May 1991 (31-05-1991)	FR2654934A1	31 May 1991 (31-05-1991)
		FR2654934B1	30 September 1994 (30-09-1994)
WO0134124A2	17 May 2001 (17-05-2001)	WO0134124A2	17 May 2001 (17-05-2001)
		WO0134124A3	10 May 2002 (10-05-2002)
		AU1146401A	06 June 2001 (06-06-2001)
		DE19953625A1	17 May 2001 (17-05-2001)
WO2005107473A2	17 November 2005 (17-11-2005)	WO2005107473A2	17 November 2005 (17-11-2005)
		WO2005107473A3	23 March 2006 (23-03-2006)
		US2008033029A1	07 February 2008 (07-02-2008)
WO2004034963A2	29 April 2004 (29-04-2004)	WO2004034963A2	29 April 2004 (29-04-2004)
		WO2004034963A3	22 July 2004 (22-07-2004)
		AT502638T	15 April 2011 (15-04-2011)
		AU2003298514A1	04 May 2004 (04-05-2004)
		AU2003298514A8	04 May 2004 (04-05-2004)
		DE602006020900D1	05 May 2011 (05-05-2011)
		DK1942891T3	26 April 2011 (26-04-2011)
		EP1942891A1	16 July 2008 (16-07-2008)
		EP1942891B1	23 March 2011 (23-03-2011)
		ES2362926T3	15 July 2011 (15-07-2011)
		HRP20110225T1	30 April 2011 (30-04-2011)
		JP2009508849A	05 March 2009 (05-03-2009)
		JP5015159B2	29 August 2012 (29-08-2012)
		PT1942891E	27 June 2011 (27-06-2011)
		RS51669B	31 October 2011 (31-10-2011)
		SI1942891T1	30 June 2011 (30-06-2011)
		TW200401649A	01 February 2004 (01-02-2004)
		US2006018839A1	26 January 2006 (26-01-2006)
		US2007053976A1	08 March 2007 (08-03-2007)
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		US8629105B2	14 January 2014 (14-01-2014)
		AT451917T	15 January 2010 (15-01-2010)
		CA2454337A1	06 August 2004 (06-08-2004)
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		ES2336091T3	08 April 2010 (08-04-2010)
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		IL154318A	31 May 2010 (31-05-2010)
		US2014121254A1	01 May 2014 (01-05-2014)
		US2014187597A1	03 July 2014 (03-07-2014)

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		EP0253490B1	22 November 1990 (22-11-1990)
		AT58473T	15 December 1990 (15-12-1990)
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		AU597670B2	07 June 1990 (07-06-1990)
		AU2673388A	15 June 1989 (15-06-1989)
		AU616449B2	31 October 1991 (31-10-1991)
		AU7422887A	17 December 1987 (17-12-1987)
		BG61200B2	28 February 1997 (28-02-1997)
		BG61201B2	28 February 1997 (28-02-1997)
		CA1318602C	01 June 1993 (01-06-1993)
		CY1578A	20 December 1991 (20-12-1991)
		DE3766308D1	03 January 1991 (03-01-1991)
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		DK302587D0	15 June 1987 (15-06-1987)
		DK302587A	17 December 1987 (17-12-1987)
		DK170514B1	09 October 1995 (09-10-1995)
		DK685888D0	09 December 1988 (09-12-1988)
		DK685888A	25 July 1989 (25-07-1989)
		DK170515B1	09 October 1995 (09-10-1995)
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		EP0320051B1	04 November 1992 (04-11-1992)
		ES2052691T3	16 July 1994 (16-07-1994)
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		GR3006220T3	21 June 1993 (21-06-1993)
		HK7997A	24 January 1997 (24-01-1997)
		HK56191A	26 July 1991 (26-07-1991)
		IE871559L	16 December 1987 (16-12-1987)
		IE60508B1	27 July 1994 (27-07-1994)
		IE883679L	11 June 1989 (11-06-1989)
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		IL82823A	10 March 1991 (10-03-1991)
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		JPS6354319A	08 March 1988 (08-03-1988)
		JPH0445B2	06 January 1992 (06-01-1992)
		JPH02209A	05 January 1990 (05-01-1990)
		JPH0667830B2	31 August 1994 (31-08-1994)
		KR950002882B1	28 March 1995 (28-03-1995)
		LV5718A4	20 February 1996 (20-02-1996)
		LV5718B4	20 June 1996 (20-06-1996)
		LV5727A4	20 April 1996 (20-04-1996)
		LV5727B4	20 October 1996 (20-10-1996)
		MX174125B	21 April 1994 (21-04-1994)
		NZ220599A	26 October 1990 (26-10-1990)
		PT85049A	01 July 1987 (01-07-1987)
		PT85049B	08 March 1990 (08-03-1990)
		PT89157A	29 December 1989 (29-12-1989)
		PT89157B	30 June 1993 (30-06-1993)
		SG52191G	23 August 1991 (23-08-1991)
		US4832957A	23 May 1989 (23-05-1989)
		US4900755A	13 February 1990 (13-02-1990)
		US4983400A	08 January 1991 (08-01-1991)
		ZA8704233A	14 December 1987 (14-12-1987)
		ZA8809189A	30 August 1989 (30-08-1989)